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09/348,354	07/07/1999	MENZO HAVENGA	4123US	5117

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EXAMINER

MARVICH, MARIA

ART UNIT PAPER NUMBER

1636

DATE MAILED: 05/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/348,354	<b>Applicant(s)</b> HAVENGA ET AL.	
	<b>Examiner</b> Maria B. Marvich, PhD	<b>Art Unit</b> 1636	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

### Period for Reply

**A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.**

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 01 March 2005.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 2,3 and 13-50 is/are pending in the application.
- 4a) Of the above claim(s) 13-32 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 2, 3 and 33-50 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>3/7/05</u> . | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

This office action is in response to an amendment filed 3/1/05. Claims 1 and 4-12 have been cancelled. Claims 2, 37, 40, 43, 46 and 50 are pending in this application. Claims 2, 33, 35, 37, 40, 43, 46 and 49-50 have been amended. Claims 13-32 have been withdrawn. Therefore, claims 2, 3 and 33-50 are under examination in this office action.

#### ***Response to Amendment***

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are no new grounds of rejection herein that were necessitated by applicants' amendment and therefore, this action is final.

#### ***Information Disclosure Statement***

An IDS filed 3/7/05 has been identified and the documents considered. The signed and initialed PTO Form 1449 has been mailed with this action.

#### ***Claim Rejections - 35 USC § 112, second paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 2 and 3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new rejection necessitated by applicants' amendment.**

Claim 2 and 3 vague and indefinite in that the metes and bounds of “tail region of the first serotype” are unclear. The first serotype provides part of a hexon and or penton. Therefore, it is unclear how the hexon or penton parts can also provide the tail region.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 3 and 33-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crystal et al (US patent 6,127,525) in view of Wickham et al (WO 96/26281). **This rejection is maintained for reasons of record in the office action mailed 3/26/03 and 12/1/04 and restated below. The rejection is slightly reworded based upon applicants' amendment.**

Applicants claim vectors comprising insertions sites for a gene of interest and a part of a fiber protein fused to the tail region of the base vector in claims 2 and 43-48. Applicants claim

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recombinant adenovirus with a capsid comprising a gene sequence encoding a part of a fiber protein adapted to exhibit a desired tropism to a plurality of target cells in a host and fused to a tail region of a fiber of the adenovirus serotype from which the recombinant vector was derived in claims 33-36 and 49. Furthermore, applicants claim methods for producing said recombinant adenovirus in claims 37-42 and 50. It is noted that claims 38 and 39 appear to the method of claim 35, which is not a method. Therefore, the claims have been interpreted to depend from claim 37.

Crystal et al teach generation of adenovirus comprising chimeric coat proteins. Specifically, Crystal et al teach that in a preferred embodiment, "a wild-type adenovirus coat protein (an adenovirus hexon and/or fiber protein) is deleted and replaced with a spacer region comprising the corresponding coat protein region of another adenoviral serotype" (see e.g. col 10, line 41-47). Specific examples are provided describing substitution of regions of the Ad2 hexon with regions from Ad40. However multiple adenoviral serotypes are contemplated serotype i.e. Ad 1, 2, 3, 5, 6, 7, 11, 12, 14, 16, 21, 34, 35, 40, 41 or 48 (column 4, line 32-41). As well, Crystal et al teach that the fiber can be deleted in part or whole and can be accompanied by modifications of the hexon (see e.g. col 11, line 48-62). Deletion of these sequences occurs by use of restriction sites, which can be naturally occurring or be introduced into the vector (see e.g. col 14, line 24-27). Hence, upon deletion of these sequences, restriction sites are left that can function as insertion sites for the fiber and hexon sequences. The wild-type vector comprises the entire adenoviral genome such as of ad5 which genome includes ITRs and packaging sequences (see e.g. col 13, line 51). Therefore, Crystal et al teach a vector comprised of an ITR and a packaging sequence from ad5 that has insertion sites for hexon and fiber (see e.g. col 11,

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line 48-62) into which can be inserted parts of fiber sequences from other serotypes such as ad35 (see e.g. col 4, line 32-41) and passenger genes (see e.g. col 17, line 52-62) as recited in part in claims 2, 43-48. Crystal et al teach methods of using the vector to generate recombinant adenovirus (see e.g. col 18, line 30-48) as recited in claims 37-42 and 50 and resulting adenoviruses as recited in claims 33-36 and 49. Crystal et al exemplify these vectors by swapping the ad7 fiber with that of ad5. In this example, ad5 is deleted of sequences 28689-31317 bp into which are inserted restriction sites PacI to BamHI. Crystal et al teach that a 1.1 kb fragment containing the Ad7 fiber gene is inserted into the deleted vector. The ability of the vector to avoid immune detection was tested in Sprague-Dawley rats and it was determined that the vector did not escape neutralizing antibodies and concluded that further deletions in combinations with these may be required.

Crystal et al do not teach that the fiber sequences are fused to the tail region of the host vector or that the chimeric fiber protein will also be responsible for exhibiting a desired tropism.

Wickham et al provide teachings that an adenovirus in which chimeric fiber proteins are generated can be used for altering the tropism of adenoviral vectors for gene therapy (see e.g. abstract). Wickham et al teach that one can advantageously practice the claimed invention by utilizing restriction sites within the native fiber coding sequence to incorporate various different nonnative receptor or protein binding domains into the chimeric fiber proteins (Examples 1-2, column 7, lines 37-61). Specifically, Wickham et al utilize an NheI site that occurs naturally within Ad5. This restriction site occurs after “the sequence coding penton base recognition domains” or the tail region (see page 24, line 20-23). Wickham teaches that restriction sites are used to remove the native fiber sequence for replacement with non-native sequences. Wickham

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stipulates that if restriction site for removal and introduction of fiber sequences, the sites flank the receptor binding sequence (see e.g. page 13, lines 23-29). The receptor binding sequences are encoded by the knob region of the fiber and are contained in the first 200 amino acids of the fiber and this is well known in the art. Specifically, Wickham teaches that "NheI site corresponds to a naturally occurring site in Ad5 fiber that occurs after the sequence coding penton base recognition domains" which region corresponds to the tail region (see page 24, line 20-23). To generate the Ad5/2 chimera, ad2 fiber is inserted into the fiber vector using an NheI to BamHI fragment and is inserted downstream of the ad5 tail region (see e.g. figure 6). Wickham is motivated to do so to utilize a naturally occurring restriction site and the resultant vector has altered tropism and antigenicity (see e.g. example 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to practice the methods of generating a chimeric adenovirus comprising an adenovirus of a first serotype and fiber sequences of Ad 1, 2, 3, 5, 6, 7, 11, 12, 14, 16, 21, 34, 35, 40, 41 or 48 as taught by Crystal et al fused to the tail region of the first adenovirus for altered tropism as taught by Wickham et al because Crystal et al teach that it is within the ordinary skill of the art to use the fibers of Ad 1, 2, 3, 5, 6, 7, 11, 12, 14, 16, 21, 34, 35, 40, 41 or 48 to generate adenoviruses with chimeric coat proteins for altered antigenicity and because Wickham et al teach that it is within the ordinary skill of the art to use chimeric fibers in which the tail region of a first adenovirus is fused to a region of a second fiber corresponding to the deleted fiber for altered tropism and antigenicity. One would have been motivated to do so in order to receive the expected benefit of wide applicability to multiple cell types that Ad 1, 2, 3, 5, 6, 7, 11, 12, 14, 16, 21, 34, 35, 40, 41 or 48 would afford as well as the benefit of utilizing the natural restriction site

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within Ad5 that does not delete the penton recognition domain but keeps this tail region intact.

Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

### ***Response to Arguments***

On pages 14-21, applicant traverses the rejections under 35 U.S.C. 103(a) over Crystal et al in view of Wickham et al in the amendment filed 3/1/05. Applicants argue the following.

1) Crystal et al do not teach that the adenovirus coat proteins can be modified by deleting and replacing a region of the coat proteins with the corresponding region from another adenoviral serotype as asserted in the office action. Applicants argue that this is because Crystal et al teach chimeric coat protein as being other than a native sequence to avoid neutralizing antibodies. Furthermore, as evidence that the resulting chimeric coat protein in Crystal et al comprised of two native sequences is contrary to the purposes of Crystal et al because it does not avoid neutralizing antibodies. 2) Applicants argue that a single generic references regarding methods of recombinant technology and adenoviral serotypes cannot be combined to generate an enabling disclosure of a chimeric fiber of the instant invention. It is applicants' arguments that in actuality, the cited passages are too widely dispersed and unrelated to the actual teachings of Crystal et al to be properly combined. 3) Crystal et al do not teach or suggest retaining the tail region from a first adenovirus serotype and stem/knob from a second. Wickham et al do not teach that the claimed adenoviral serotypes produce a different tropism or provide the missing teachings or suggestions to overcome the teaching away of Crystal et al. Gall et al provided as

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evidence of altered tropism is said by applicants not to demonstrate that the Ad5/Ad7 fibers have altered tropism. Instead, it is concluded that Wickham et al teaches that all of the fibers are interchangeable except Ad3 and altered tropism is only demonstrated by insertion of nonnative sequences such as RGD. 4) Wickham et al do not provide motivation for the retention of the tail region by use of NheI. Absence of a detrimental effect does not adequately provide the motivation to extrapolate its use to any adenovirus. 5) Rhea et al and Havenga et al are provided as evidence that the instant invention represent a major breakthrough and would not have been found obvious.

Applicant's arguments filed 3/1/05 have been fully considered but they are not persuasive. 1) Applicants appear to be arguing that Crystal et al intend by non-native sequences to be non-adenoviral sequences. However, Crystal et al teach explicitly, "a wild-type adenovirus coat protein (an adenovirus hexon and/or fiber protein) is deleted and replaced with a spacer region comprising the corresponding coat protein region of another adenoviral serotype" (see e.g. col 10, line 41-47). And in col 11, line 56-59, Crystal et al teaches, "In particular, preferably the fiber protein can be replaced in its entirety, or in part, with sequences of a fiber protein from a different serotype of adenovirus. This is followed in col 16 by the statement that "of course the chimeric adenoviral coat proteins include coat proteins in which native (i.e. wild-type) hexon and/or fiber proteins are replaced by a hexon and or fiber amino acid sequence of a different adenovirus serotype such that the resultant adenovirus vector has decreased ability or inability to be recognized by neutralizing antibodies" (line 5-11). Therefore, it is clear that Crystal et al intended to generate chimeric fibers comprising sequences of two different adenoviruses. Furthermore, that the ad5/7 virus does not escape neutralizing antibodies does not teach away

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from using these disclosed chimeric fiber proteins. Rather, Crystal et al surmise that to completely avoid neutralizing antibodies, deletions of epitopes outside of the fiber region may be desirable (see col 25, line 15-28). This conclusion is hardly unexpected given that neutralizing antibodies are generated against any available epitope. The results in fact speak to maintaining the swapped fibers and deletion of regions of the hexon in concert. Furthermore, the inability of avoiding neutralizing antibodies does not address whether the altered fibers have altered antigenicity. The bar for avoiding neutralizing antibodies is quite high while altered antigenicity must only be demonstrated by a change in the antigenicity.

2) Crystal et al are drawn as a whole to a method of generating chimeric adenovirus. To this end, the cited passages while separated in the specification are all drawn to describing the invention of Crystal et al, that of swapping regions fibers and/or hexons between adenovirus. For instance, col 14 teaches explicitly methods of deleting and replacing regions of fiber or hexon to this end. Specifically, Crystal et al state, "convenient restriction sites (which can be further introduced into a sequence) can be used to introduce or remove segments of DNA, or other genes or coding sequences" (line 25-27).

3) Crystal et al do not explicitly teach retention of the tail region for generation of the chimeric fibers. Instead Crystal et al teach that convenient restriction sites can be used to insert the non-native sequences. Wickham explicitly states that any region can be swapped as long as the receptor binding regions are deleted and replaced. As success of this statement, Wickham demonstrates that use of a restriction site in the tail region can be used as a site of deletion and insertion of non-native sequences. Based upon the successful incorporation of non-native sequences into the tail region, the high skill of one of ordinary skill in the art, and absent

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evidence to the contrary, a person of skill in the art would have concluded that restriction site similarly placed in the fiber could be used to insert non-native sequences. In fact, applicants have relied upon similar results to extrapolate that the tail region is adequate and successful for functional alignment of the non-native sequences. Applicants have based the limitation that the tail region can be retained from the native ad5 fiber from a single image in the specification, figure 6 to all fibers. Wickham et al teach methods of altering targeting of the adenovirus (tropism) by generation of chimeric fiber proteins (see page 7, line 21-29). Contrary to applicants' arguments, Wickham teaches that differences in the fibers can be exploited to alter targeting and structural similarities between the fibers can also be exploited to generate the actual chimeras. This fact actually speaks to the conservation of the restriction site within the tail region to generate the altered fibers. Much of Wickham is directed to alteration of the native adenovirus fiber with sequences from other adenoviral serotypes. For example, "an Ad3 fiber amino acid sequence or the entire Ad3 fiber 3expressed in an Ad5 chimeric fiber protein or in place of an Ad5 fiber protein respectively is a "nonnative amino acid sequence" bridging sentence page 9-10. And, ""Chimeric fiber protein" is intended to include a fiber protein of a serotype, which differs from that of the adenovirus on which it is expressed" (page 10, line 25-27). Applicants argue that because the Ad5 and Ad7 fibers have overlapping receptors, that the tropism of the ad5/ad7 chimera has not been altered. In fact, Gall does demonstrate altered tropism with the chimeric receptor as evidenced by the following statements. "Therefore by replacing the fiber gene in the chimeric construct, we have redirected the virus to a high-affinity receptor which is normally used for attachment by Ad7A" (see Gall, Journal of Virology, Vol 7, No. 4, April 1996, page 2119, col 2, paragraph 3 and page 2120, col 2, paragraph 1). "We have

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found rat epithelial cell lines that are refractory to slAd5NCAT-F7 but can be infected by dlAd5NCAT” (page 21221,col 2, paragraph 1). These results are used to conclude, “the strategy in this study can be extended to replace the Ad5 fiber with fiber from any given serotype” (page 2121, line 1-4). It is clear that applicants recognize that ability to redirect viruses by generating chimeric fibers.

5) The statements of Rea et al are not directed at describing a breakthrough in generating chimeric fibers with the ability to have altered tropism. Rather, Rea et al describe the development of vaccines and in directing genes toward dendritic cells given that authors belief that dendritic cell transfer itself is an essential goal in gene therapy. This statement does not speak to the nonobviousness of the present invention but a subset of inventions based upon the technology of altering tropism by replacement of fibers. Similarly, Havenga et al are interested in altering tropism for the express purpose of infecting SMCs and ECs. The instant claims are not drawn to infection of SMCs, ECs or DCs. Rather, the instant invention recites broadly, the altering of any adenoviruses by insertion of fiber sequences from Ad 1, 2, 3, 5, 6, 7, 11, 12, 14, 16, 21, 34, 35, 40, 41 or 48. This technology is obvious given the teachings of Crystal et al that teach methods of swapping fibers in view of Wickham et al that teach that adenovirus with swapped fibers can have altered tropism.

### ***Conclusion***

No claims are allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).


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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
GERRY LEFFERS  
PRIMARY EXAMINER

Maria B Marvich, PhD  
Examiner  
Art Unit 1636

May 12, 2005